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Food and Drug Administration
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SUPPLEMENT TO CITIZEN PETITION

REGULATORY STATUS OF SYNTHROID® ORALLY ADMINISTERED

LEVOTHYROXINE SODIUM USP

Docket No. 97N-0314/CP2

In its Citizen Petition, Knoll Pharmaceutical Company ("Knoll") demonstrated that Synthroid® brand orally administered levothyroxine sodium USP is generally recognized as safe and effective ("GRAS/E") for replacement or supplemental therapy in hypothyroidism.[1] This supplement discusses how the Food and Drug Administration's recently published review package explaining the reasons for the agency's approval of a new drug application (NDA) for Unithroid levothyroxine sodium (the "review package")[2] bolsters the case that Synthroid is generally recognized as safe and effective. This supplement also submits additional data and analyses demonstrating that Synthroid is generally recognized as safe and effective on the basis of the kinds

1. Citizen Petition on Regulatory Status of Synthroid® Orally Administered Levothyroxine Sodium USP, Docket No. 97N-0314/CP2, filed Dec. 15, 1997 and supplemented May 29, 1998 and November 17, 1999 (hereinafter "GRAS/E Petition" or "Petition"). The Petition as previously supplemented is incorporated by reference in this supplement. Unless otherwise noted, references to exhibits in the Petition refer to materials filed on Dec. 15, 1997 and are cited herein as "Petition Exhibit __."

2. <http://www.fda.gov/cder/drug/infopage/unithroid/unithroid.htm> (last modified Aug. 29, 2000).

of clinical endpoints discussed in the review package.

Knoll recounted in its GRAS/E Petition the well-known and well-accepted logic of using exogenous levothyroxine as a replacement for endogenous thyroxine in hypothyroidism. In brief, when the thyroid produces too little thyroid hormone (thyroxine), many tissues and metabolic processes are affected, causing numerous clinical manifestations such as fatigue, lethargy, cold intolerance, dry skin, bradycardia, and hoarseness.[3] Low levels of thyroxine also cause an increase in the serum levels of thyroid stimulating hormone (TSH) (also called thyrotropin). Measurement of serum TSH is therefore the cornerstone of the diagnosis of primary hypothyroidism. Likewise, the normalization of TSH is the goal of treatment; the clinical manifestations of hypothyroidism generally improve along with the normalization of the serum TSH although not necessarily at the same rate.[4]

FDA's discussion in the review package of hypothyroidism and its causes, diagnosis, and treatment for the most part parallels Knoll's discussion in the Petition. The Medical Officer Review ("MOR"),[5] for example, begins by describing the proposed indication for the NDA, an indication which is essentially the same as the indication for which Knoll seeks GRAS/E status for Synthroid.[6] Under the heading REVIEW OF BASIC AND CLINICAL PHARMACOLOGY OF THYROID HORMONES, the MOR discusses the effects of thyroid

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3. Exogenous levothyroxine and endogenous thyroxine (T4) are both metabolized in the body to triiodothyronine (T3), which exerts the effects on cells causing such clinical manifestations. For convenience, this supplement, like the GRAS/E Petition, previous supplements, and the review package, skips the T4 to the T3 step.

4. Petition at 4-6.

5. <http://www.fda.gov/cder/drug/infopage/unithroid/morred.pdf> (July 21, 2000).

6. Compare MOR at 4 with Petition at 1-2.

hormones, including thyroxine, on numerous tissues and metabolic processes,[7] and under the heading of CLINICAL SIGNS AND SYMPTOMS, provides a list of clinical effects which is similar to Knoll's list.[8] Likewise, under the heading REGULATION of THYROID HORMONE SECRETION, the MOR describes the T4/TSH feedback system in terms comparable to Knoll's: when T4 levels go down, TSH goes up, and vice versa.[9]

Also paralleling Knoll's discussion, the LABORATORY EVALUATION section of the MOR advises diagnosis of hypothyroidism by a sensitive TSH assay, and goes on to say that "Serum TSH alone may be used (provided a sensitive TSH assay is used) to monitor therapy for primary (thyroidal) hypothyroidism because a linear inverse correlation exists between serum TSH and free T4."[10] The MOR reiterates the importance of TSH in an extensive paraphrase of the American Thyroid Association's treatment guidelines, including the key

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7. MOR at 5-6.

8. Compare MOR at 8-9 with Petition at 5.

9. Compare MOR at 5 with Petition at 4-6.

10. MOR at 9.

statement that dosage should be titrated to the point at which "the serum TSH level is normalized."[11]

Like Knoll's Petition, the review package, including the MOR, textbooks, the published literature, and the views of virtually every expert in the field, reflect certain medical and biological facts:

1. If levels of thyroxine are inadequate, the patient's TSH increases and he or she may also have signs and symptoms of hypothyroidism.

2. Because TSH is a sensitive and universal bioassay for levothyroxine levels, clinicians rely on tests of TSH as a key means of diagnosing hypothyroidism and assessing whether TSH has been normalized. They do so because they know that if TSH levels have been normalized, levothyroxine levels are adequate, and that therefore signs and symptoms of hypothyroidism will resolve if they have not already done so.

For these reasons, experts agree that an adequate and well-controlled study which shows that a particular levothyroxine drug product normalizes TSH is an appropriate study to assess the efficacy of such a levothyroxine drug product. The experts whose declarations were submitted with Knoll's Citizen Petition relied on adequate and well-controlled published

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11. MOR at 10. The Petition also relies on and discusses the ATA treatment guidelines. Petition at 4 and 12. Indeed, the lead author of the ATA treatment guidelines, Peter Singer, M.D., is one of the experts who has concluded that Synthroid is generally recognized as safe and effective. See Declaration of Peter A. Singer, M.D., Petition Exhibit 4. See also Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association Guidelines for Detection of Thyroid Disfunction. Arch Intern Med 2000;160:1573-75. ("Serum TSH assay is an accurate, widely available, safe, and relatively inexpensive diagnostic test for all common forms of hypothyroidism[.]").

Copies of the Ladenson et al. article and other publications referred to in this Supplement and in expert declarations and reports attached to it are attached as Exhibit 1. Articles in Exhibit 1 are ordered alphabetically by first author.

studies showing that the correct dose of Synthroid normalizes TSH.[12]

Without explaining why, however, the MOR's analysis headed DEMONSTRATION OF CLINICAL EFFECTIVENESS OF LEVOTHYROXINE does not mention as a basis for concluding that Unithroid is effective the ability of levothyroxine sodium drug products to control or normalize TSH, a curious omission in light of the review package's discussion of and emphasis on the importance of TSH in diagnosing hypothyroidism and evaluating the adequacy of replacement therapy with levothyroxine sodium.[13] Perhaps the applicant did not mention this point, or perhaps studies of this point are referenced by implication in the phrase "examples of well-controlled clinical efficacy studies include . ."[14] Whatever the reason, Knoll emphasizes that adequate and well-controlled studies which demonstrate that a levothyroxine drug product normalizes TSH are an appropriate basis for a conclusion that a levothyroxine

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12. See Declarations of Drs. Wartofsky, Spencer, Davies, Singer, and Finkel, Petition Exhibits 5, 3, 6, 4, and 10.

13. The text in question reads:

> The majority of clinical studies in the literature have not been designed to demonstrate that levothyroxine is effective per se, but rather to define what best constitutes the optimal euthyroid state in terms of biochemical surrogate endpoints of thyroid function (TSH, total and free T4 and total and free T3), end organ physiologic effects (e.g. cardiovascular hemodynamic endpoints: left ventricular ejection fraction, cardiac output, systemic vascular resistance, etc.) and clinical outcomes. Examples of well-controlled clinical efficacy studies include those by Cooper et al (Ann Int Med 101:18-24, 1984) and Monzani et al (Clin Invest 71:367-71, 1993) who demonstrated statistically significant improvement in the Billewicz Clinical Index, cardiac contractility and neuropsychological symptoms (e.g. memory impairment, anxiety, depression) in patients with subclinical hypothyroidism who were treated with levothyroxine compared to controls.

MOR at 16.

14. Indeed, the MOR's BIBLIOGRAPHY lists studies which do use TSH normalization as an endpoint (e.g., Fish et al., Number 76).

product is generally recognized as safe and effective, and for an NDA as well.[15]

Although Knoll and most experts believe that studies using normalization of TSH as the endpoint are the best way to assess efficacy of levothyroxine drug products, Knoll and leading experts also believe that Synthroid is generally recognized as safe and effective on the basis of adequate and well-controlled studies using "clinical"and other biochemical endpoints. As discussed in the Further Declarations of Leonard Wartofsky, M.D., Carole Spencer, Ph.D, F.A.C.B., Peter A. Singer, M.D., and Terry F. Davies, M.D.,[16] Synthroid is generally recognized as safe and effective on the basis of published, adequate and well-controlled studies demonstrating that Synthroid is effective in improving hypothyroidism-related myocardial

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15. Please note in this regard that the MOR is incorrect in suggesting that a study of the "optimal euthyroid state" cannot also demonstrate that levothyroxine is effective per se. MOR at 16. Discussion continues in the clinical community about the optimal levels of TSH, but whatever TSH level a clinician posits as "optimal," if a study shows that a particular dose of LT4 suppresses TSH to that level, the study has, in fact, demonstrated the efficacy of the levothyroxine product in addition to providing data on the question of optimality. See Further Declaration of Leonard Wartofsky, M.D., a copy of which is attached hereto as Exhibit 2.

16. Exhibits 2, 3, 4, and 5, copies of which are attached hereto.

dysfunction,[17] dyslipidemia,[18] and altered ventilatory responses.[19] Drs. Davies, Singer, Spencer, and Wartofsky, as well as Dr. Marion J. Finkel, agree that these published studies are adequate and well-controlled.[20]

In sum, not only is Synthroid generally recognized as safe and effective on the basis of studies using normalization of TSH levels as the endpoint for proof of efficacy, it is also

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17. Bough EW, Crowley WF, Ridgway EC, Walker H, Maloof F, Myers GS, et al. Myocardial Function in Hypothyroidism. Relation to Disease Severity and Response to Treatment. Arch Intern Med 1978;138:1476-1480, and Crowley WF, Ridgway EC, Bough EW, Francis GS, Daniels GH, Kourides IA, et al. Noninvasive Evaluation of Cardiac Function in Hypothyroidism. Response to Gradual Thyroxine Replacements. N Engl J Med 1977;296:1-6. The levothyroxine sodium product in each study was Synthroid. Letter from E. Chester Ridgway, M.D., Professor of Medicine and Head, Division of Endocrinology, Metabolism and Diabetes, University of Colorado Health Sciences Center, to Steven P. Weinstein, M.D., Ph.D., Knoll Pharmaceutical Company (October 9, 2000), a copy of which is attached as Exhibit 6.

18. Liu, XQ, Rahman A, Bagdade JD, Alaupovic P, Kannan CR. Effect of Thyroid Hormone on Plasma Apolipoproteins and ApoA- and ApoB-Containing Lipoprotein Particles. Eur J Clin Inv 1998;28:266-70.

19. Ladenson PW, Goldenheim PD, Ridgway EC. Prediction and Reversal of Blunted Ventilatory Responsiveness in Patients with Hypothyroidism. Am J Med 1988;84:877-83.

20. Exhibits 5, 4, 3, 2, and Further Declaration of Marion J. Finkel, M.D., attached hereto as Exhibit 7. Other adequate and well-controlled studies relied on by one or more of the thyroid experts are: Ladenson PW, Stakes JW, Ridgway EC. Reversible Alteration of Visual Evoked Potential in Hypothyroidism. Am J Med 1984;77:1010-1014, and Hussein WI, Green R, Jacobsen DW, Faiman C. Normalization of Hyperhomocysteinemia with L-Thyroxin in Hypothyroidism. Ann Intern Med 1999;131:348-351. A majority of all patients in the homocysteine study were treated with Synthroid. Interoffice memorandum from Steven P. Weinstein, M.D., Ph.D., Knoll Pharmaceutical Company, to Tim Seaton, M.D. (Oct. 11, 2000), a copy of which is attached hereto as Exhibit 8. See also Yarboro CM, Loys LA, Minor JR, Weintraub BD, Steinberg AD Miller FW. Thyroxine Replacement Improves Clinical and Laboratory Parameters In Patients With Subclinical Hypothyroidism and Theumatic Disease, Arthritis and Rheumatism 1990;33:S131 (Abstract C157) (In randomized, double-blind placebo-controlled study conducted by clinicians at the National Institutes of Health, the Synthroid group had "significantly lower symptom scores (many patients had decreased mentation and menstrual difficulties, and less fatigue); physical exam scores (less edema, dry skin and delayed reflexes); global disease activity indices; mean TSH (3.3 v. 7.5 U/ml) and cholesterol (198 v. 250 mg/dl) values.").

generally recognized as safe and effective on the basis of other studies using as proof of efficacy clinical and biochemical endpoints such as myocardial function, ventilatory responses, and levels of plasma cholesterol and other lipoproteins.

Conclusion

For the reasons stated in the Petition, previous supplements, and this supplement, Knoll Pharmaceutical Company renews its request that FDA grant the relief sought by its Citizen Petition.

Environmental Impact

Petitioner claims a categorical exclusion from the requirement of an environmental impact assessment under 21 C.F.R. § 23.30(a) and, by analogy, § 25.31(a).

Certification

The undersigned certify that, to their best knowledge and belief, this supplement includes all information and views upon which the supplement relies, and that it includes representative data and information known to the petitioner which are unfavorable to the supplement.

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